CIPAC Guideline for analytical methods for the determination of relevant impurities referred to in FAO and/or WHO specifications for pesticide technical grade active ingredients and formulations

Scope
This document describes the processes for development, evaluation and adoption and publication of peer validated methods by CIPAC for the determination of relevant impurities in pesticide active ingredients and, where relevant, in formulations as defined in FAO/WHO specifications.

Introduction
The FAO and the WHO invited CIPAC to consider independent laboratory validations (ILV) for relevant impurities in the scope of its activities.
CIPAC agreed to accept the request made by the FAO and the WHO to deal with ILV for relevant impurities defined in FAO/WHO specifications, since CIPAC sees the need for such methods. It was decided that the method validation and development should be handled in principle as CIPAC methods for substances, as there is no need to deviate from former procedures.
The methods, the results and the statistical evaluation thereof should be discussed and possibly adopted at CIPAC meetings. The CIPAC chairman will inform the WHO and the FAO on the decisions.
Adopted methods, if necessary with remarks from CIPAC, will be made available on the CIPAC website. The methods will not be covered by CIPAC copyrights in the strict sense\(^1\), although the methods will also be published in CIPAC handbooks.
There will be no "provisional" or "full" status for analytical methods for the determination of relevant impurities in technical material or formulations.\(^2\)

Developing a method prior to peer validation
As with methods for the determination of the content of pesticide active ingredients, a draft impurity method needs some supporting data which should be generated in-house to demonstrate to a certain extent the reliability of the method to be tested later. This set of data will most probably be generated by the laboratory that has developed the method. The data presented should provide sufficient information on the following points:

- Confirmation of analyte identification by suitable method
- Specificity: to be shown for technical material and all proposed formulation types

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\(^1\) This means that these methods are in the public domain and available by download, in contrast to „normal“ methods which are charged for.

\(^2\) It should be noted that it is not the intention of CIPAC to interfere with data requirements that are set for national authorisations of pesticides. This guidance document is linked to FAO and WHO specifications.
• **Calibration**: minimum duplicate determination for three concentrations. One concentration should be the specified limit.

• **Accuracy**: minimum of 2 recovery determinations at the level specified in the FAO/WHO specification. Standard additions are acceptable. To be done for technical material and all relevant formulation types.

The individual recovery rates should be within the following ranges [SANCO/3030/99][1]:

<table>
<thead>
<tr>
<th>Content [%]</th>
<th>Recovery [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt; 1</td>
<td>90-110</td>
</tr>
<tr>
<td>0.1-1</td>
<td>80-120</td>
</tr>
<tr>
<td>&lt; 0.1</td>
<td>75-125</td>
</tr>
</tbody>
</table>

• **Repeatability**: minimum of 5 replicates at the level specified in the draft FAO/WHO specification. To be done for technical material and all relevant formulation types. In cases where the specified limit in the formulation is linked to the content of the active ingredients, only the lowest value needs to be validated. For the assessment the modified Horwitz equation should be used [2].

• **The limit of quantification** (LOQ) of the method(s) must be determined for technical material and all relevant formulation types. It is necessary to specify in a validation note exactly how the limits have been determined.

This set of data must also be provided to the laboratories participating in the ILV and to CIPAC. These data are also assessed by CIPAC together with the data described below.

**Peer validation through CIPAC network**

The validation should be conducted as a validation study with a minimum of 3 independent laboratories. The laboratories chosen to conduct the trials must not have been involved in the method development and in its subsequent use. Provided this criterion is met, one of the laboratories chosen to conduct the trial may belong to the applicant’s organisation. In contrast to a CIPAC full trial following criteria should be met by each laboratory:

• **Specificity**: to be shown for technical material and all proposed formulation types

• **Calibration**: minimum duplicate determination for three concentrations. One concentration should be the specified limit.

• **Accuracy**: minimum of 2 recovery determinations at the level specified in the FAO/WHO specification. Standard additions are acceptable. To be done for technical material and all relevant formulation types. The criteria for the assessment are as described above.
• **Repeatability**: minimum of 5 replicates at the level specified in the draft FAO/WHO specification. To be done for technical material and all relevant formulation types. The criteria for the assessment are as described above.

• The **LOQ** of the method(s) must be determined for technical material and all relevant formulation types. It is necessary to specify in a validation note exactly how the limits have been determined.

The reproducibility as defined in relevant publications cannot be determined by a minimum of 3 laboratories participating in such a validation study. However, the modified Horwitz equation can be used to judge on the robustness of the method\(^3\).

The invitation to the study could go through the existing CIPAC network (CIPAC information sheets), but it is not mandatory to do so. As soon as the method and the in-house validation are available, the organiser could contact the CIPAC secretary and chairman. After a preliminary check of the method and the in-house validation data and possible clarification of open points, the CIPAC secretary would send out information with the announcement of a peer validation in the form of a small scale study. As usual, the information sheet contains data like the active ingredient involved, methodology, instrumentation, number of samples and the deadline for sending back the results of the analyses.

Laboratories which are interested in participating would then contact the organiser, who in turn ships the method, the samples and the required reference materials to the selected laboratories.

Alternatively, such a study may also be initiated by the company itself or through a country PAC. However, the validation criteria would remain the same.

After receiving the results of the participating laboratories, the organiser prepares a draft method in CIPAC style and a report, containing the statistical data and the names and comments of the participating laboratory. The organiser usually presents the method and the evaluation at the following CIPAC meeting to allow discussion and possible adoption of the method by CIPAC.

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On behalf of CIPAC

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Chairman of CIPAC    CIPAC Secretary    CIPAC Member

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\(^3\) Being aware that methods used in monitoring laboratories possibly needs to be validated according to their own requirements.
References

[2] Modified Horwitz equation:

\[
\%\text{RSD}_r < 2^{(1 - 0.5 \log C)} \times 0.67
\]

where C = concentration of the analyte in the sample as a decimal fraction.